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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: NAS 0; Not Product Specific
General Correspondence: Other
Comments on Draft Guidance for Industry: PHARMACOKINETICS IN PREGNANCY - STUDY DESIGN, DATA ANALYSIS, AND IMPACT ON DOSING AND LABELING [Docket 2004D-0459]

Dear Sir or Madam:

Enclosed please find comments from GlaxoSmithKline on the draft 'Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling'. We appreciate the opportunity to provide comments on this draft guideline and generally agree with the content. Overall we find the guidance to be comprehensive, clinically appropriate, and well-articulated. Specific comments are provided on subsequent pages, organized under the same section headings as used in the draft guidance and cross-referenced by line number.

This submission is provided in paper and electronic format according to the instructions provided at http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm?AGENCY=FDA.

Please contact me at (919) 483-6405 or my colleague Robin O'Connor-Semmes, at (919) 483-4056, if you require clarification or have questions about these comments. Thank you for your consideration.

Sincerely,

Anne N. Stokley, M.S.P.H.
Director, Policy, Intelligence & Education
US Regulatory Affairs

2004D-0459 C4

Comments on Draft Guidance for Industry: Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling

General comments:

- Although the guidance explicitly doesn't intend to pursue neonatal safety, as stated in the introduction on page 4, additional data collection with permission from well-studied, motivated mothers with PK data would prove clinically valuable. One key area that would naturally follow from clinical pharmacology studies in pregnant women is exposure of drug to the fetus/neonate. Our suggestion is to add a section encouraging the following:
  - Amniotic fluid drug concentrations (if PK sampling is done for other reasons)
  - Venous and arterial umbilical cord drug concentrations at birth
  - Venous sampling in neonate at birth and some time period post birth
  - Post-delivery breast milk concentration would also be useful
  - Link mother's and neonate's PK through further assessment of placental transporters, metabolizing enzymes, etc.
  - Sparse PK sampling in neonate, since neonate exposure is an important part of the overall safety profile of a compound used in pregnancy.
- The PK/PD approach is only of value if there is an established PK/PD relationship in the general population; otherwise the results are less informative. Discussion on sample size, page 8, says dose adjustments based on PK alone, so one could dispute the need for dynamic measures.
- With regard to metabolic probe substrates, a drug interaction study with a concomitant medication of concern may be of more value than a probe approach.
- The use of matched controls requires time, money and exposure of additional subjects to drug. We encourage comparisons to historic data already collected in healthy men and women within the existing program.

Specific recommendations, annotated to each section of the draft guidance:

III. DECIDING WHETHER TO CONDUCT A PHARMACOKINETIC STUDY IN WOMEN

Line 165 (conditions under which PK study is recommended): "Pregnancy is likely to alter significantly the PK of a drug (e.g. renally excreted drug) and any of the above apply". It would be useful to have the FDA position regarding a situation where the drug is likely to be used in pregnancy, but the PK is not expected to be altered (e.g., cleared via a pathway know to remain relatively unchanged in pregnancy). If the recommendation is to perform the study anyway (e.g., because it is a drug that will be used in pregnant women), then the bullet point of line 165 (above) should be omitted.

VI. DATA ANALYSIS

A. Parameter Estimation

Line 404: Recommend removal of reference to Vz/F (leave as Vss/F), due to Vz/F dependence on CL. It may be best not to encourage use of Vz/F.

B. Development of Dosing Recommendations

Line 416-424: Collecting unbound AUC may be too high of a sampling and analytical hurdle when developing dosing recommendations. We suggest comparing parent and metabolite exposures and let unbound exposure be secondary, not primary as stated in the guidance. Unbound concentrations could be measured at peak and trough concentrations to reduce complexity and burden.

VII. LABELING

A. Clinical Pharmacology

1. *Pharmacokinetics Subsection*

Recommend that the Pharmacokinetics section of the Clinical Pharmacology section contain data which are limited to healthy volunteers and/or the primary patient population of interest. In most cases, this will not include pregnant patients. Thus, in most cases, pharmacokinetic data from pregnant patients would be best presented under "Special Populations" only.

2. *Special Populations Subsection*

If no pharmacokinetic studies have been conducted in pregnant patients, we recommend that the "Pregnancy" section under "Special Populations" be omitted, rather than stating "No studies have been conducted in pregnant patients." This statement would be included under the "Precautions: Pregnancy" section of the label (as noted in section VII.B. of the draft guidance, Precautions/Pregnancy).